

### **REMARKS**

In response to the Official Action dated May 20, 2004, Applicant respectfully submits the present Amendment and Remarks. Pursuant to 37 CFR 1.111, reconsideration is respectfully requested.

Claims 21 to 35 are currently pending in this application. Claims 21 to 26 have been amended, and new claims 27 to 35 have been added to the application, in order to more distinctly claim various embodiments of the invention.

Support for amendment specifying the fusion protein of the invention is "antigen-binding" may be found throughout the specification (e.g., page 7, lines 9 to 21) and the claims as originally filed. Other amendments to the claims are for the purpose of more specifically defining the invention.

The Examiner has required amendment to the specification to update the relationship between the present application and the parent case. The present Amendment updates this relationship, specifically referring to the parent application as having issued as U.S. Patent 6,238,667 on May 29, 2001.

The Examiner has also required that the Abstract of the Disclosure be shortened. The present Amendment replaces the original Abstract with a shortened version. No new matter has been added. Applicant respectfully submits that the Abstract is now in full compliance with 37 CFR 1.72 and MPEP §608.01(b).

Relying on 35 USC §112, first paragraph, the Examiner rejected claims 21 to 26, alleging that the subject matter thereof does not enable a person skilled in the art to make and use the invention commensurate in scope with the claims. The Examiner further alleges that it would require undue experimentation for one skilled

in the art to practice the invention as claimed. Applicant respectfully traverses this rejection.

Applicant submits that the present specification provides highly detailed guidance in teaching those skilled in the art how to make and use the invention. Moreover, Applicant respectfully submits that the skilled artisan following the teachings in the specification could practice the claimed invention with routine, if any, experimentation. The Examiner's attention is respectfully directed to, for example, the specification at page 4, lines 7 to 25; pages 10 to 14; and the Examples, wherein methods for creating a fusion protein under the invention are disclosed. Applicant submits that these examples clearly teach those skilled in the art how to practice the invention as claimed and, as such, that the application is fully enabled.

The Examiner further alleges that the specification does not teach how to make and use "all fusion protein made up of any antibody and any peptide, without the amino acid sequence, and all nucleic acid encoding all undisclosed antibody and undisclosed peptide."

Applicant respectfully points out that the invention as presently claimed is not limited to a fusion protein with any particular peptide (or amino acid sequence). Rather, the fusion proteins in various embodiments of the invention include a peptide possessing homophilic, immuno-stimulatory and/or membrane transport activities, where the peptide does not interfere with antigen binding. The skilled artisan can readily determine whether said peptide comprises one or more of the aforementioned activities.

In a similar fashion, the invention as presently claimed is not meant to be limited to any particular antibody binding specificities, immunoglobulin heavy or light

chains or cellular receptor on a normal or a tumor cell. Rather, the invention as presently claimed can be used in a myriad of combinations, the details of which are known to those skilled in the art. Applicant respectfully submits that the specification provides the necessary guidance to apply the invention to each of these various combinations under the practice of the invention.

The Examiner further objects to the recitation of a "gene" in the previously presented claims. While Applicant is of the position that one skilled in the art understands the terminology as originally used in the claims, in the interest of advancing prosecution Applicant has amended to the claims to recite a "nucleic acid fusion product".

The Examiner relies on Stryer et al. as teaching that "the primary amino acid sequence determines the conformational [sic] of the protein." Applicant, however, is not claiming the conformation of proteins. Rather, the invention as presently claimed features fusion proteins comprising (1) an antibody and (2) a peptide possessing homophilic, immuno-stimulatory and/or membrane transport activity, where the peptide does not interfere with antigen binding, regardless of the specifics of the protein conformation.

The Examiner relies on Ngo et al., alleging that this reference teaches "the amino acid positions within a polypeptide/protein that can tolerate change ... which are critical to maintain the protein's structure/function will require guidance." Applicant respectfully submit that the application as filed, including the references cited therein, provides sufficient guidance as to the construction of fusion proteins under the invention.

The Examiner relies on Kuby et al. as teaching "antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into [a] specific conformation that contribute[s] to binding."

Applicant respectfully reiterates that the invention as presently claimed features fusion protein comprising (1) an antibody and (2) a peptide with homophilic, immuno-stimulatory and/or membrane transport activities, where the peptide does not interfere with antigen binding, regardless of the particulars the fusion protein conformation.

The Examiner further relies on Abaza et al. as teaching "a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site."

However, the invention as presently claimed is not directed to single amino acid substitutions outside of antigenic sites. Rather, the invention as presently claimed is directed to a antigen-binding fusion protein comprising an antibody and a peptide possessing homophilic, immuno-stimulatory and/or membrane transport activities.

The Examiner next alleges that "... it is unpredictable which peptide when fused to the antibody has which particular biological activity, in turn, would be useful for any purpose."

Applicant respectfully submits that the choice of particular antibody and particular peptide comprising homophilic, immuno-stimulatory and/or membrane transport activity, is known to the skilled artisan, and the fusion protein of the invention as presently claimed is more than adequately described in the application.

For at least the reasons detailed above, Applicant respectfully submits that the application as filed provides the guidance that permits one skilled in the art to make and use the invention as claimed. Applicant respectfully reminds the Examiner that the specification need not, and indeed preferably does not, exemplify all possible embodiments of the invention. Rather, the specification need only provide the necessary guidance to the skilled artisan in order to allow them to make and use the invention. Applicant respectfully submits that he has more than adequately provided such guidance in the present application.

As the specification is fully supportive of the invention as presently claimed, Applicant respectfully requests the Examiner reconsider and withdraw this rejection under 35 USC §112, first paragraph.

Relying on 35 USC §112, first paragraph, the Examiner rejected claims 21 to 26, alleging that the subject matter thereof does not convey that the inventor had possession of the claimed invention at the time the application was filed. Applicant respectfully traverses this rejection.

Applicant respectfully submits that the application as filed fully describes and exemplifies the claimed invention. As such, there can be no doubt that Applicant had possession of the claimed invention at the time the application was filed.

The Examiner further alleges that the specification does not provide an adequate written description of the invention. Applicant respectfully disagrees with the Examiner's position.

The invention as presently claimed features fusion proteins which, in various embodiments of the invention, comprise an antibody and a peptide comprising homophilic, immuno-stimulatory and/or membrane transport activity. Description of

each of these embodiments of the invention are provided in the specification as filed (including the references incorporated therein).

In light of the above, Applicant respectfully requests the Examiner reconsider and withdraw this rejection under 35 USC §112, first paragraph.

Relying on 35 USC §112, second paragraph, the Examiner rejected claims 21 to 26, alleging that the subject matter thereof is indefinite. Applicant respectfully traverses this rejection.

The Examiner alleges that it is unclear what is meant by "homophilic activity". Applicant respectfully submits that the meaning of the term "homophilic" is well known to the skilled artisan, and respectfully directs the Examiner's attention to, for example, the paragraph bridging pages 25 and 26 of the specification.

The Examiner also objects to the wording "the composition" in original claims 24 to 26, as lacking antecedent basis in base claim 23. The amendment to claims 24 to 26 obviates this grounds for rejection.

The Examiner has further objected to the wording "inverse hydropathicity" as recited in claim 26. Applicant further respectfully submits that the term is fully understood by those skilled in the art to which the invention pertains. Moreover, the Examiner's attention is respectfully directed to, for example, the paragraph bridging pages 25 and 26 in the specification (and U.S. Patent 5,523,508 incorporated therein by reference). Applicant thus respectfully submits that the term "inverse hydropathicity" is within the state of the art and, as such, is not indefinite.

For at least the reasons given above, Applicant respectfully submits that the invention as presently claimed is more than adequately and definitely described in

the application as originally filed. Applicant thus respectfully requests the Examiner to reconsider and withdraw this rejection under 35 USC §112, second paragraph.

Relying on 35 USC §102(b), the Examiner rejected claims 21 to 23, 25 and 26, alleging that the subject matter thereof is anticipated by U.S. Patent 5,314,955. Applicant respectfully traverses this rejection.

Applicant first notes that U.S. Patent 5,314,955 is not of record in this application. Applicant is thus of the belief that the Examiner is referring to U.S. Patent 5,314, 995, which is of record. Applicant's remarks that follow are based upon this belief.

The invention as presently claimed has one embodiment wherein the peptide portion of the fusion protein comprises a homophilic activity. The cited patent neither teaches nor suggests a fusion protein containing such a peptide moiety, and thus cannot anticipate claims including this feature.

In another embodiment of the invention as presently claimed, the fusion protein includes a peptide comprising a membrane transport activity. Applicant respectfully submits that the cited patent neither teaches nor suggests a fusion protein comprising a peptide with a membrane transport activity, and therefore does not and can not anticipate claims directed to this embodiment of the invention.

In yet another embodiment of the invention as presently claimed, the peptide portion of the fusion protein comprises an immuno-stimulatory activity. Applicant respectfully submits that the fusion construct described in the cited patent is not shown to have an immuno-stimulatory activity. As such, the cited patent cannot anticipate the claims directed to this embodiment of the present invention.

The Examiner has included claim 26 in this rejection, alleging that "IL-2 is an immunogenic peptide that inherently has an inverse hydropathicity plot." The Examiner has cited no document of record to support his allegation of inherency. Applicant respectfully reminds the Examiner that he has the burden of providing evidence in the record to support his position; a mere statement of inherency is insufficient. Applicant therefore respectfully requests the Examiner to provide documentary evidence supporting his contention that IL-2 inherently has an inverse hydropathicity plot or, alternatively, withdraw this grounds for rejection of claim 26.

In light of the above, Applicant respectfully submits that U.S. Patent 5,314,995 does not anticipate the invention as presently claimed. Applicant therefore respectfully requests the Examiner to reconsider and withdraw this rejection under 35 USC §102(b).

Relying on 35 USC §102(b), the Examiner rejected claims 23 and 24, alleging that the subject matter thereof is anticipated by U.S. Patent 5,698,679. Applicant respectfully traverses this rejection.

In the invention as presently claimed, claims 23 and 24 are directed to an embodiment wherein the fusion protein includes a peptide comprising a homophilic activity. Applicant respectfully submits that U.S. Patent 5,698,679, neither teaches nor suggests such a fusion protein, such that the invention as presently claimed is not, and can not be, anticipated by the cited patent. Reconsideration is respectfully requested.

Applicant notes that in paragraph 16 of the Official Action, the Examiner indicates that the application currently names joint inventors. However, the application currently names a single inventor. Applicant respectfully requests



acknowledgement in the next Official Action that Dr. Heinz Kohler is the sole listed inventor of record in the U.S. Patent and Trademark Office for the present application.

Relying on 35 USC §103(a), the Examiner rejected claims 21 to 26, alleging that the subject matter thereof is unpatentable over US. Patent 5,314,995, in view of Dempsey et al., Tao et al., Bhattacharya-Chatterjee et al or WO96/20219. Applicant respectfully traverses this rejection.

The deficiencies in the disclosure of U.S. Patent 5,314,995, with respect to the invention as presently claimed are discussed above, and incorporated by reference into Applicant's response to this rejection.

First, the Examiner states that the invention as claimed in claims 21, 23 and 24 "differs" from the disclosure of US Patent 5,314,995. Applicant respectfully submits that where the claimed invention differs from the disclosure of the cited document, there can not properly be a rejection of anticipation over that document. As such, the rejection of these claims under 35 USC §102(b), discussed above, should properly be withdrawn.

Regarding the 35 USC §103 rejection, Applicant respectfully directs the Examiner's attention to the invention as presently claimed. In certain embodiments (present claims 21 to 27), the invention features a fusion protein including a peptide comprising homophilic activity. Applicant respectfully submits that none of the cited references teach or suggest such a fusion protein. As such, Applicant respectfully submits that the cited references, taken alone or in combination, cannot render this embodiment of the invention obvious to one of ordinary skill in the art.

Another embodiment of the invention (present claims 32 to 35) features a fusion protein including a peptide comprising a membrane transport activity. Applicant respectfully submits that none of the cited references, taken alone or in combination, teach or suggest such a fusion protein. As such, claims directed to this embodiment of the invention can not be rendered obvious to one of ordinary skill in the art in light of the references.

Yet another embodiment of the invention as presently claimed (claims 28 to 31) features a fusion protein comprising (1) an antibody and (2) a peptide comprising an immuno-stimulatory activity wherein the peptide does not interfere with antigen binding.

Dempsey et al. describe a HEL-C3d fusion. Neither hen egg lysozyme (HEL) nor C3d is an antibody. As such, the fusion of Dempsey et al. is not an antibody-peptide fusion product, and Dempsey et al. does not teach or suggest such an antibody-peptide fusion product.

Tao et al. (Abstract) is directed to the fusion of a tumor-derived idiotypic to GM-CSF. The referenced Abstract is silent on the fusion as being an antigen-binding fusion protein as in the invention as presently claimed.

The Examiner cites Bhattacharya-Chatterjee et al. as teaching an anti-idiotypic antibody. The document, however, does not teach or suggest the combination of features of the invention as presently claimed.

Similarly, the Examiner alleges that WO 96/20219 discloses various antibodies such as anti-idiotypic antibody 3H1. This publication, however, also fails to teach or suggest the antigen-binding fusion protein comprising (1) an antibody and

(2) a peptide having immuno-stimulatory activity where the peptide does not interfere with antigen binding as in the invention as presently claimed.

The Examiner alleges that motivation exists to combine the publications in the way he has done by merely restating the alleged teaching of these documents. The Examiner does not, however, point to specific motivation for the combination of documents stated within the four corners of the documents. Applicant respectfully submits that documents applied in combination need not only teach certain features of the claimed invention, they must also in and among themselves, provide the motivation to one of ordinary skill in the art to make the claimed combination. Applicant respectfully submits that the cited documents fail to make such a disclosure. As such, Applicant respectfully submit that this rejection of the claims is improper, and respectfully requests reconsideration and withdrawal of this rejection.

At page 11, first paragraph, of the Official Action, the Examiner states that claim 26 is included in this rejection because the immunogenic C3d peptide would have been expected to be "hydrophilic or inverse hydrophobicity" within the length of the peptide. The Examiner provides no evidence on the record to support this allegation. Applicant respectfully submits that a proper rejection can not merely be based upon an unsupported allegation by the Examiner. The Examiner must provide documentation to support such statements when rejecting the claims. As there is no such documentation of record that the Examiner points to, Applicant respectfully submits that this grounds for rejection is also improper and request that it be withdrawn.

Relying on 35 USC 103(a), the Examiner rejected claims 21 to 26 over US Patent 5,314,995, in view of Rojas et al. and Bhattacharya-Chatterjee et al. (J.

Immunology 145: 2758-2785 (1990)) or WO96/20219. Applicant respectfully traverses this rejection.

Applicant's position regarding the shortcomings in the disclosure of US Patent 5,314,995 is discussed above, and incorporated by reference in reply to this rejection.

Notwithstanding the rejection of claims 21 to 23 over U.S. Patent 5,314,995 under 35 USC §102(b) discussed above, the Examiner admits that the invention as claimed in claims 21 and 23 "differs from the teachings of the reference...." As such, the Examiner has again admitted on the record that the rejection above under 35 USC §102(b) (as it pertains to claims 21 and 23) is improper, since an alleged anticipation cannot be found where the invention as claimed differs from the disclosure of the cited reference. Thus, the rejection of these claim (above) under 35 USC §102(b) should properly be withdrawn.

The Examiner cites Rojas et al., as disclosing a cell membrane translocating sequence. However, the invention as presently claimed features not only a peptide component comprising a membrane transport activity, but also an antibody component. Rojas, et al. is concerned with EGF activation and mimicking phosphorylated EGF receptor. Rojas et al. does not disclose an antibody moiety and, as such, does not teach or suggest the combination of features in the invention as presently claimed.

The Examiner cites the Bhattacharya-Chatterjee et al. publication for allegedly teaching an anti-idiotypic antibody such as 3H1. Applicant's position regarding the disclosure of this publication is set forth supra, and incorporated by reference in response to this rejection.

The Examiner cites WO 96/20219 for allegedly teaching various antibodies such as anti-idiotypic antibody 3H1, as well as a pharmaceutical composition. Applicant's position regarding the disclosure of this publication is set forth supra, and incorporated by reference in response to this rejection.

In one embodiment, the invention as presently claimed features a fusion protein including (1) an antibody and (2) a peptide comprising a homophilic activity. None of the documents cited by the Examiner, taken alone or together, teach or suggest such a combination of features. As such, the rejection as directed to this embodiment (present claims 21 to 27) of the invention should be withdrawn.

In another embodiment, the invention as presently claimed features a fusion protein including (1) an antibody and (2) a peptide comprising a membrane transport activity. Again, none of the cited publications, taken alone or in combination, teach or suggest such a fusion protein. Therefore, the rejection as directed to this embodiment (present claims 32 to 35) of the invention should be withdrawn.

In yet another embodiment, the invention as presently claimed features a fusion protein including (1) an antibody and (2) a peptide comprising an immunostimulatory activity. To the extent that Rojas et al. has not been discussed previously with respect to this embodiment of the invention, Applicant respectfully submits that the publication does not teach or suggest a fusion protein including an antibody and a peptide comprising an immunostimulatory activity (EGF is not an antibody). Applicant's response concerning the other cited documents have already been discussed previously with respect to this embodiment of the invention. As none of the cited documents, taken alone or together, teach or suggest this

embodiment (claims 28 to 31) of the invention, the rejection as applied to the subject matter of these claims should also properly be withdrawn.

The Examiner alleges a motivation to combine the disclosure of the references by again merely reiterating the alleged teachings of the cited documents. The Examiner does not point to any teaching or suggestion disclosed in any of the documents themselves that would motivate one of ordinary skill in the art to the claimed combination of the invention. Applicant respectfully submits that it is not enough that the cited documents may individually mention one of various features of the claimed invention. Rather, the documents must also provide the motivation for one of ordinary skill in the art to combine their disclosures. Applicant respectfully submits that the cited documents fail to provide such a motivation for the invention as presently claimed in this application.

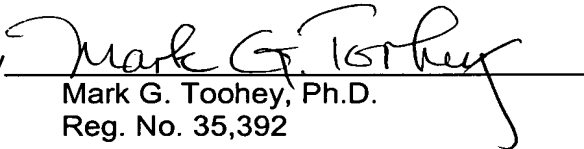
Moreover, Applicant respectfully submits that the Examiner is "picking and choosing" pieces of the cited documents in fashioning this rejection. As such, the Examiner appears to be making this rejection under 35 USC §103(a) with the benefit of hindsight, after reading the disclosure of the instant application. Such a reliance upon hindsight, after perusing Applicant's disclosure, is "impermissible." For this reason also, this (and the previous) rejection of the claims under 35 USC §103(a) should be withdrawn. Reconsideration is respectfully requested.

In light of the foregoing amendments and remarks, Applicant respectfully submits that the application is now in condition for allowance. Should any minor matter remain, or should the Examiner feel that an interview would expedite the prosecution of this application, the Examiner is invited to call the undersigned at his convenience.

To the extent necessary, Applicants petition for an extension of time under 37 CFR 1.136. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to the Antonelli, Terry, Stout & Kraus, LLP Deposit Account No. 01-2135 (Docket No. 411.35629PC2), and please credit any excess fees to such Deposit Account.

Respectfully submitted,

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## **APPENDIX**